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Psychological Interventions as They Relate to Intrusive Thinking

Intrusive, Emotional Mental Imagery after Traumatic and Negative Events

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Abstract

Common across psychological disorders, intrusive, emotional mental images are sensory-perceptual representations that intrude involuntarily into the mind. Mental health treatments typically focus on entire disorders with multiple symptoms. This chapter suggests focusing on core clinical symptoms (i.e., intrusive imagery). Existing psychological therapy techniques (e.g., imagery rescripting) are promising, but underlying treatment mechanisms need to be better understood.

Precise treatments and preventions are required. Using the example of psychological trauma, this chapter argues that psychological interventions can be developed in the laboratory: effective experimental analogues of trauma can generate intrusions so that putative interventions that modulate intrusions can be explored at various mechanistic levels (e.g., molecular, cognitive, social). Examples of targeting "new" (i.e., Day 1 of the traumatic event) memories include a simple cognitive interference intervention that holds promise for preventing intrusive images after trauma (a behavioral protocol including *Tetris* game play). This intervention specifically targets intrusive involuntary memories while leaving voluntary memory intact. Work on targeting "old" (as of Day 2) memories is at an earlier stage. Research on reconsolidation update mechanisms appears valuable in reducing older trauma memories via interference interventions, again with a behavioral task interference technique. To understand mechanisms across different levels (e.g., molecular, cognitive, or social), mathematical models can aid the identification of causal mechanisms involved in memory formation. Questions are posed to instigate discussion of future science-driven psychological interventions for intrusive images.

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Introduction

What Is Intrusive Thinking?

One of the rare clinical psychology textbooks dedicated to intrusive thinking (Clark 2005:4) states:

> we define unwanted clinically relevant intrusive thoughts, images or impulses as any distinct, identifiable cognitive event that is unwanted, unintended, and recurrent. It interrupts the flow of thought, interferes in task performance, is associated with negative affect, and is difficult to control.

In this chapter, we focus on intrusive thoughts in the form of mental images. This is because intrusive images occur across mental disorders. Further, it has been shown that, compared to verbal thought, imagery has a more powerful impact on emotion (Holmes and Mathews 2010) and thus carries the most weight in psychopathology. We suggest that a focus on mental imagery opens up novel angles for treatment innovation.

Mental images are sensory-perceptual representations; that is, like perception in the absence of percept (Pearson et al. 2015), as if "seeing in the mind's eye." They can occur in any sensory modality, not just visual. Imagery can be of past memories or simulations of future events. When images intrude involuntarily into the mind, they can carry strong emotion and influence behavior.

Intrusive image-based memories of a traumatic event are a core clinical feature of both acute stress disorder and posttraumatic stress disorder (PTSD) (American Psychiatric Association 2013). For instance, a person who experienced a traumatic road traffic accident may develop a distressing intrusive image of a red truck coming toward them right before the accident happened (Iyadurai et al. 2018). Mothers who have experienced traumatic childbirth may see an intrusive image of the hospital lights above them when they went into surgery (Horsch et al. 2017).

Intrusive images are not only present after trauma, such as in PTSD, they can appear in numerous other psychological disorders (Holmes and Mathews 2010). For instance, people with social phobia may repeatedly see themselves performing badly in a social situation, and such negative self-images play a causal role in maintaining symptoms in social phobia. People with depression may experience intrusive images of themselves being rejected or socially isolated, whereas they usually experience impoverished positive future imagery (Hales et al. 2011; Newby and Moulds 2012; Holmes et al. 2016a). Intrusive mental imagery may act as an emotional amplifier of all mood states in people with bipolar disorder (Holmes et al. 2016b): Vivid negative mental imagery, such as seeing oneself committing suicide in the future, may drive despair. Vivid overly positive imagery, such as seeing others responding extremely well to one in social situations, may drive mania. These are only some examples of intrusive images across mental disorders; the list could even be

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further extended to account for intrusive imagery in obsessive-compulsive disorder (OCD) (Coughtrey et al. 2015), body dysmorphic disorder (Osman et al. 2004), and agoraphobia (Day et al. 2004).

Here, we focus on intrusive mental imagery associated with psychological trauma and depression. Thus, the mechanisms, treatments, and mathematical framework discussed may or may not apply to other psychological disorders characterized by intrusive images, such as OCD, which we do not address in detail.

What Are Psychological Interventions?

Psychological therapy is described as an interpersonal intervention, usually provided by a mental health professional, such as a clinical psychologist who employs any of a range of psychological techniques. Various schools of therapy include cognitive behavioral therapy (CBT), psychoanalysis, systemic therapy, and so forth. The CBT model was derived from a combination of principles from behavioral and cognitive psychology alongside clinical experience. In brief, CBT focuses on challenging and changing unhelpful cognitive distortions (e.g., thoughts, beliefs, and attitudes) and behaviors and improving emotional regulation. The individual learns personal coping strategies to solve current problems. The therapist assists the individual in identifying strategies to address goals and improve symptoms. CBT asserts that maladaptive thoughts and behaviors influence the development and maintenance of psychological disorders, and thus symptoms can be reduced through new information-processing skills and coping strategies.

Is there evidence that these methods actually work? Critically, how do we choose which psychological or pharmacological intervention to use? Evidence-based guidelines, such as put out by the U.K. National Institute for Health and Care Excellence (NICE), critically review the full clinical literature and make recommendations on the basis of how effectively treatments work. There have now been hundreds of trials of psychological treatments. These can be classified by mental disorder; in the case of intrusive thinking, PTSD provides an example.

From such a review of the clinical research evidence, the main recommendation for PTSD, in terms of a first-line treatment, is individual *trauma-focused cognitive therapy* (National Institute for Health Care Excellence 2018). This is a tailored form of cognitive behavioral psychological therapy which follows a clear, validated manual; typically 8–12 sessions, each an hour long, are held with a mental health professional who is highly trained in its specific delivery. It includes elaboration and processing of the trauma memories, processing trauma-related emotions, and restructuring trauma-related meanings for the individual. The evidence-based guidelines for PTSD also recommend another psychological treatment: *eye movement desensitization and reprocessing*. CBT interventions can also be targeted at specific symptoms, such as sleep disturbance or anger. Drug treatments are only recommended as a secondary approach if patients prefer drugs over therapy (National Institute for Heath and

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Care Excellence 2018), as the evidence is less strong for clinical effectiveness. Drug treatments after trauma are not recommended as a preventive strategy; in particular, benzodiazepines can worsen symptoms.

Since the inception of CBT in the 1960s, great advances have been made. For instance, we now have highly effective evidence-based CBT treatments for full-blown PTSD. This is one of the areas in which we have the best treatments: some of the best PTSD trials have recovery rates of 75%, whereas the norm in CBT is 50% (Holmes et al. 2014). However, there are still many ways in which we need to improve psychological treatments (Holmes et al. 2018). How can we adapt or simplify them to reach more people? How do we understand the critical ingredients in a psychological treatment in so doing? Can we also "prevent" rather than "cure"? That is, can we prevent intrusive memories after trauma rather than only have treatments once the full-blown disorder has been established?

When we think, we can think in the form of words (verbal thought) or mental images (sensory representations in any modality such as visual, olfactory, or auditory images). The dominant focus in psychological treatment research and therapy, such as CBT, has been on verbal thoughts. A focus on *mental imagery* is one alternative and may open up opportunities for both research and treatment innovation.

What Can We Do at the Moment?

CBT Techniques That Target Intrusive Mental Imagery

In a handbook for clinicians and patients, we have described four face-to-face mental imagery-focused techniques in CBT: imagery rescripting, metacognitive techniques, imagery-competing tasks, and enhancement of positive imagery (Holmes et al. 2019). In contrast to the CBT techniques that typically focus on a whole disorder (rather than on one symptom), these techniques specifically focus only on distressing intrusive mental images. During imagery rescripting, a person is asked to bring an intrusive negative image to mind and describe it in detail (e.g., an image of oneself in a car crash). An alternative image is then introduced to transform and update the negative image (e.g., an image of oneself being well today despite the car crash). Metacognitive techniques aim at lessening an image's impact on a person by emphasizing that it is not real (e.g., switching attention from the internal image to the outside world or reinforcing the image's unreality by making it look comical). Imagery-competing techniques aim at disrupting or interfering with intrusive images with a competing task (e.g., a visuospatial computer game) while the image is active in a person's mind. Positive imagery enhancement aims at encouraging people to generate positive future images or repeatedly train them to interpret ambiguous scenarios in a more positive way (Holmes et al. 2019).

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Need to Understand Psychological Interventions in the Lab and Be Able to Disseminate Them Globally

To understand how existing treatments for intrusive images work, we need to clarify the key mechanisms driving these treatments. An experimental psychopathology approach allows a direct test of whether an experimental manipulation of a specific mechanism leads to a change in intrusions where key processes that maintain or change aspects of psychopathology can be identified. Thus, we need to take current treatments back to the laboratory and examine specific treatment mechanisms modulating intrusions in isolation and under controlled conditions. We can then remove irrelevant strategies from current treatments and develop novel approaches that target the essential causal mechanisms modulating intrusive images and are more effective and precise (Holmes et al. 2018). Such novel approaches need to be easily scalable to meet the global need for mental health treatments. Thus, we need to develop simple, brief, and flexible interventions that can be adapted to people's needs across cultures. Such interventions should ideally not require highly trained mental health professionals but should be able to be delivered by trained lay mental health care workers via innovative and remotely accessible online platforms (Holmes et al. 2018).

What Do We Need to Do Next?

Research Paradigms to Study and Generate Intrusions

To improve treatments that target intrusive thinking, we need to be able to generate intrusions and study their crucial underlying mechanisms in controlled laboratory settings. Going back to the lab allows us to change focus from complex real-life situations with clinical populations to simpler experimental procedures with nonclinical human (or nonhuman) populations (Visser et al. 2018). That is, we need experimental models that incorporate the dynamic nature of intrusive memories (Visser et al. 2018). Different paradigms can be used to generate intrusions in the laboratory. Here, we focus on two commonly used analogs of stressful events/trauma in anxiety and PTSD research: fear conditioning (Pittig et al. 2018) and the trauma film paradigm (James et al. 2016a).

Fear Conditioning

One well-known experimental method to investigate involuntary expressions of aversive memory in both human and nonhuman animals is Pavlovian fear conditioning. This paradigm has been used to investigate aversive associative learning, considered to be an important mechanism in the etiology of anxiety disorders (Pittig et al. 2018). Indeed, in real-life settings, learning what is threatening or safe is important for survival. However, the association of

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neutral cues with threat can become maladaptive when such conditioned fear fails to extinguish long after the danger has passed or overgeneralizes to a wider range of contexts.

Fear-conditioning paradigms allow for an investigation of the emergence, persistence, and resurgence of maladaptive fear responses (Pittig et al. 2018). It has been suggested that intrusion, hyperarousal, and hypervigilance symptoms, which characterize PTSD, may arise as a result of conditioned fear responses (for a review, see Norrholm and Jovanovic 2018). Note, however, that fear-conditioning experiments have mainly investigated arousal or hypervigilance (e.g., skin conductance, startle reflex–fear responses) that are mostly relevant to anxiety disorders.

Intrusions, however, are the hallmark feature of PTSD, which is no longer classified as an anxiety disorder but as a trauma- and stressor-related disorder in DSM-5 (American Psychiatric Association 2013). As fear-conditioning paradigms do not specifically account for the image-based episodic nature of intrusive thoughts (Visser et al. 2018), it remains an interesting open question whether this paradigm could also be used to generate intrusive memories of a stressor in the laboratory. A more ecologically valid and clinically relevant experimental model may be needed to generate and study intrusions per se in the laboratory.

Trauma Film Paradigm

In the trauma film paradigm, participants are asked to view a composition of short, distressing film clips with traumatic content (James et al. 2016a). This paradigm has been shown to induce intrusive memories to clips of the film (i.e., with image-based episodic nature).

Trauma is defined as exposure to death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence (American Psychiatric Association 2013). Notably, in addition to *direct* exposure (e.g., as a victim or witness), repeated or extreme *indirect* exposure to aversive details of trauma, usually over the course of work (e.g., when a police officer has to *view pictures* of murder), is now included as part of the diagnostic criterion for what comprises a traumatic event in the DSM-5 (American Psychiatric Association 2013). This recent inclusion of indirect exposure to trauma underscores the ecological validity of the trauma film paradigm (James et al. 2016a).

Of note, intrusive memories can also be induced by overly positive film stimuli (Davies et al. 2012) or depression-linked film material (Lang et al. 2009). Thus, the trauma film paradigm is not only useful for studying intrusive images related to PTSD but also for studying intrusive thinking in depression or bipolar disorder.

In studies using the trauma film paradigm, intrusive memories of the film are usually monitored in a paper-and-pencil diary directly when they occur

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over the course of daily life (James et al. 2016a). This method records intrusion frequency data over longer time frames and carefully matches intrusions to the trauma film (participants usually record whether they had an intrusion or not for several time periods per day over the course of one week and briefly describe each intrusion's content). Mixture models can be a useful tool to analyze such diary data because they model intrusion and non-intrusion data differently (see discussion on mechanisms and mathematics below for further details).

Additional Methods

Watching visual stills of distressing content (e.g., injured people) has also been shown to generate intrusions two days later (Battaglini et al. 2016). In addition, listening to negative arousing stories while watching a slide show of pictures can generate negative emotional memories (Galarza Vallejo et al. 2019).

Levels of Mechanism to Modulate Intrusive Emotional Images

Using controlled and standardized experimental procedures and the possibility to focus on specific clinical targets is an essential step toward understanding complex clinical disorders (Visser et al. 2018). Once one has successfully generated intrusions in the laboratory, it is possible to study specific mechanisms that could modulate them (e.g., reduce intrusion frequency or distress/vividness of intrusions). At this point it is important to note that such intrusions can be modulated at any level of mechanism (e.g., molecular, cognitive, or social). Here we discuss examples of paradigms modulating intrusions at various levels: pharmacological approaches operating at the molecular level, visuospatial interference interventions operating at the cognitive level, social support operating at the social level, and other examples such as sleep and wakeful rest.

Molecular Level: Pharmacological Approaches

Pharmacological approaches may offer a way to modulate intrusive memories. For instance, inhibiting N-methyl D-aspartate receptor (NMDAR)-dependent memory consolidation through antagonistic drugs may reduce the frequency of intrusive memories after trauma. In line with this idea, inhaling the NMDAR antagonist gas nitrous oxide (N_2O) shortly after a laboratory analog of trauma *fastened* the reduction of intrusive trauma-related memories compared to inhaling medical air over the course of the following week. Of note, N_2O led to an increase in intrusion frequency in those individuals who were highly dissociated at baseline, urging caution regarding the use of N_2O in dissociated individuals (Das et al. 2016).

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Cognitive Level: Visuospatial Task Interference

Research in cognitive psychology and experimental psychopathology has shown that cognitive interference interventions (memory orientation/reminder cue and visuospatial task) may be a promising technique to reduce both the frequency of intrusive images as well as the level of distress and vividness associated with them (Iyadurai et al. 2019). The working mechanisms behind this intervention are based on three assumptions:

1. Intrusive memories can be altered shortly after an event or at retrieval (Visser et al. 2018).
2. The capacity of people's working memory is limited (Baddeley 2003).
3. Visuospatial tasks occupy working memory resources that would be needed to (re)consolidate intrusive mental images (James et al. 2015).

Thus, engaging in a visuospatial task such as a visuospatial computer game like *Tetris* (James et al. 2015; Iyadurai et al. 2018), or a complex finger tapping exercise, at a time when mental images of the event are active, may disrupt these distressing images. It is hypothesized that the intervention works because the two processes compete for visual processing resources and the brain cannot attend equally to the distressing image and the visuospatial task. Importantly, such task interference has to take place at a time when the memory is labile and vulnerable to alteration (McGaugh 2000; Nader 2003).

Even though visuospatial interference interventions have mostly been investigated in relation to distressing trauma memories, they also work with overly positive material (Davies et al. 2012). This suggests that the mechanisms apply to intrusive emotional memories in a more general sense rather than only to trauma-related intrusive images.

Social Level: Social Support

There has been an increased interest in the impact of social factors on emotion regulation. Both human and nonhuman experiments have shown that the presence of another during an aversive experience may work as a buffer by reducing fear responses (Thorsteinsson and James 1999; Mikami et al. 2016). Experiences of social support could increase the process of learning what is *safe* in the environment (social safety learning) through social support interactions, which in turn decrease stress reactivity to stressful experiences (Ditzen and Heinrichs 2014).

After a psychologically traumatic event, social support (i.e., supportive interactions with family and friends) is believed to be associated with having fewer posttraumatic cognitions (e.g., trauma-related thoughts and beliefs), which in turn is associated with PTSD symptoms (Woodward et al. 2015). These results signal a need to investigate social interactions and social support

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after a negative or stressful experience as a potential causal mechanism for the development or maintenance of psychological disorders and to study this in the laboratory. For example, if the absence of social support after trauma leads to people having more intrusions, whereas perceived social support causes people to have less intrusions, we could specifically target this mechanism in future preventive treatments for people who experienced a traumatic event.

Studying the mechanisms at a social level may have relevance for public mental health. Brief and low-intensity social support interventions may not need to be delivered by highly trained professionals but could instead be implemented by members of the public. *Social prescription* refers to the idea of linking patients in primary care with sources of support within the community, for instance, enabling health care professionals to refer patients to a service provided by the voluntary and community sector alongside existing treatments to improve health and well-being (Bickerdike et al. 2017). In line with the idea of social prescription, social support interventions including emotional, instrumental, and informational support could be delivered by volunteers (e.g., hospital volunteers) who are already present in many medical facilities, thus allowing us to scale up preventive interventions.

Other Levels: Sleep or Wakeful Rest

An example of how memory could be boosted rather than blocked is wakeful rest (Dewar et al. 2014). A brief wakeful rest period after learning may actually *enhance* memory in the short (after 15 minutes) and long term (after seven days) compared to performing a nonverbal task (note that these studies tested participants' declarative memory). The wakeful-resting period is thought to boost recently acquired memories by isolating the memory trace of the story (or nonwords) from competing memories, making the memory easier to retrieve at a later stage (Dewar et al. 2014). These results confirm the crucial role of the memory consolidation period in the strengthening of new memories, here through spontaneous reactivation during wakeful resting.

What remains to be further explored is the possible involvement of similar processes in the maintenance of intrusive thoughts during the consolidation period of emotional material. Wakeful rest might actually be what trauma patients usually do when waiting for medical care in the emergency department after a traumatic experience. Thus, investigating the effects of wakeful rest on intrusive memories after a traumatic event could have clinical implications and guide the development of future interventions. In line with this idea, a few studies have already investigated the role of sleep and sleep deprivation after trauma on intrusive memories (e.g., Porcheret et al. 2015, 2019, 2020). As these initial investigations revealed mixed results, further research on the role of sleep and wakeful rest as candidates to modulate intrusive memories is clearly warranted.

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Modulating the Frequency of Intrusive Memories: From Lab to Clinic

New Memories of a Traumatic Event

By "new" we refer to Day 1 of the (experimental or real) traumatic event. Intrusive memories of trauma have a clear onset (i.e., the time of the traumatic event), making them amenable to study. This allows us to investigate ways to intervene with the initial memory consolidation of a problematic image before it causes further distress at any of the above described levels of mechanism, such as the molecular level (Das et al. 2016).

Several studies using the trauma film paradigm (James et al. 2016a) indicate that after the experimental trauma (30 min or 4 hr), performing a brief cognitive interference intervention (comprised of a memory orientation/reminder cue, mental rotation instructions, and playing the visuospatial computer game *Tetris*) reduces intrusive images compared to not performing any task (e.g., Lau-Zhu et al. 2019). Two proof of principle randomized control studies have recently extended this effect to a clinical setting that involves (a) road traffic accident survivors who are waiting in the emergency department (Iyadurai et al. 2018) and (b) mothers who experienced traumatic childbirth (Horsch et al. 2017), both within the first six hours after the traumatic event.

Psychological interventions for traumatic memories should ideally interfere with the involuntary, intrusive aspect of a memory but should not impair voluntary memory expression (Lau-Zhu et al. 2019). A person who has experienced sexual abuse by a piano teacher would, for instance, not want images of the abuse to intrude on their mind involuntarily, whereas they may want to be able to recall episodes and facts about the event when required for legal reports (see Figure 14.1). Experimental studies in the laboratory make it possible to investigate such a distinction. Findings suggest that a visuospatial interference task intervenes with the involuntary (intrusive) memory, whereas the voluntary memory remains intact when controlling for potential other task characteristics (Lau-Zhu et al. 2019).

This data raises the intriguing possibility that intrusive image-based memories are in fact "special" and can be selectively targeted by visuospatial interference interventions, whereas voluntary memory remains unaltered (Lau-Zhu et al. 2019). In contrast to traditional single trace theories of memory, which argue that involuntary and voluntary memories are derived from the same memory system, this data conforms to *separate trace theories*, stating that different memory traces underlie involuntary and voluntary memories. Thus, intrusive reexperiences may be supported by a specialized perceptual memory system that is functionally dissociable from the episodic memory system supporting voluntary recall of the same event, in line with dual representation theory (Brewin 2014). Visuospatial interference intervention (e.g., reminder cue and *Tetris*) may then preferentially disrupt this sensory-perceptual memory system, whereas the episodic memory system remains unaffected (Lau-Zhu et al.

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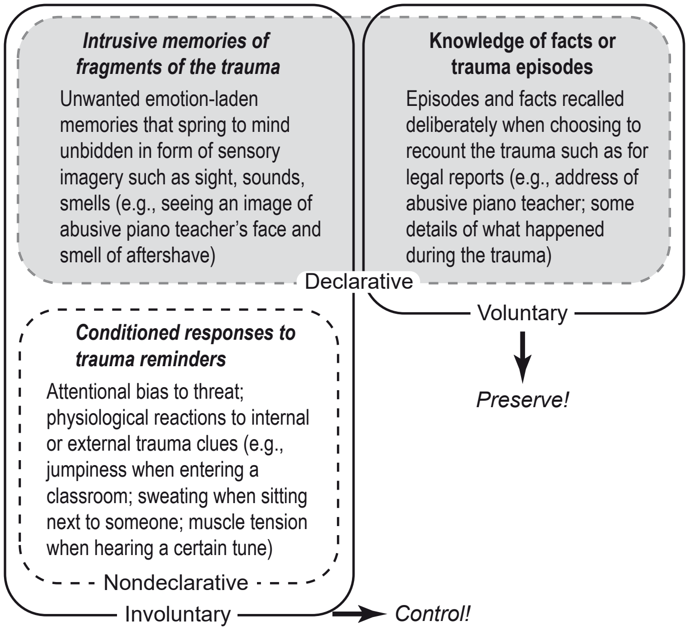

Figure 14.1 Diagram depicting how different memory systems may represent various aspects of a traumatic event (e.g., sexual abuse by a piano teacher). In general, clinically beneficial interventions should aim to target the maladaptive involuntary expression of trauma memories (e.g., intrusive memories) while preserving its voluntary recall (e.g., ability to testify in court). Adapted after Visser et al. (2018).

2019). In contrast to widely used fear-conditioning paradigms, the trauma film paradigm may be particularly useful to assess these different aspects (readouts) of trauma memory in the laboratory (Table 14.1). Future work is warranted.

Old Memories of a Traumatic Event

By "old" we refer to Day 2 onward of the (experimental or real) traumatic event, and in one study many years later. Most work discussed above has focused on the time window that is thought to overlap mainly with (synaptic) consolidation. Consolidation refers to a strengthening of local neural circuits via a cascade of molecular processes involving protein synthesis and the formation of new synaptic connections necessary for a memory to persist in the long term. As illustrated above, interventions delivered during this time period (i.e., minutes to hours after an event) are able to interfere with the newly formed memory and reduce its intrusiveness (McGaugh 1966, 2000). Promisingly, recent research suggests that, under the right circumstances, even established memories can be modified. Rather than there being a one-off opportunity, memories can, upon their retrieval, enter a transient labile state; that is, they

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Table 14.1 Overview of different aspects of trauma memory that can be targeted and associated research approaches, from animal models (bottom) to clinical populations (top). Left: different levels at which trauma can be modeled. Middle: potential targets for intervention. Right: memory readouts: (1) occurrence of intrusive images (e.g., diary, provocation task), (2) event details (e.g., interview), (3) learning episode details (e.g., recognition test), (4) self-report of symptoms, (5) rating of subjective distress, (6) unconditioned stimulus expectancy, (7) attentional bias, (8) approach/avoidance behavior, (9) noninvasive physiology, (10) invasive physiology. Note: voluntary memory recall (e.g., trauma details) can be measured in humans but is not the key clinical target of a treatment. Adapted after Visser et al. (2018).

Level	Targets	Memory readouts
Complex real-life emotional memory, PTSD patients: • Heterogeneous, possible multiple or sustained trauma exposure • Clinical >1 month posttrauma	• Intrusive image-based memories or other experiences (DSM5 cluster B) • Physiological reactivity to internal/external reminders (DSM5 cluster B) • Unwanted avoidance of internal/external reminders (DSM5 cluster C) • Negative mood/cognition (DSM5 cluster D) • Hyperarousal (DSM5 cluster E) • Functional impairment (DSM5 cluster G)	1, 2, 4, 9
Simpler real-life emotional memory, humans • Single trauma exposure soon after event • Simple phobia • Possibly subclinical	• Intrusive images • Subjective distress • Unwanted avoidance • Physiological reactivity Associated with (reminders of) specific real-life situations	1, 2, 4, 6–9
Complex experimental emotional memory, humans • Trauma analog from viewing of aversive film clips	• Intrusive images • Subjective distress • Physiological reactivity Associated with (reminders of) aversive lab stimuli	1, 3, 5, 9
Simpler experimental emotional memory, humans • Aversive conditioning, still pictures paired to electric shocks	• Subjective distress • Avoidance • Physiological reactivity Associated with conditioned cues and contexts	3, 5–9
Simpler experimental emotional memory, nonhuman animals: • Fear conditioning, tones paired to electric shocks	• Avoidance • Physiological reactivity Associated with conditioned cues and contexts	8–10

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can become malleable again (e.g., Sara 2000; Alberini 2005; Nader and Hardt 2009). The restabilization of a memory is a putative process termed memory reconsolidation (Nader et al. 2000). This process is dependent on *de novo* protein synthesis; interventions that directly or indirectly target this process thus have the potential to change maladaptive emotional memories (Milton and Everitt 2012), including those giving rise to intrusive images of trauma. Figure 14.2 depicts different time windows of memory malleability.

Different interventions can interfere with the reconsolidation of a memory on different levels. On a molecular level, fear-conditioning studies in rodents have shown the potential of pharmacologically disrupting one-day-old (Nader et al. 2000; Lee et al. 2006; Ortiz et al. 2015) and even one-month-old (Gräff et al. 2014) memories, resulting in a persistent attenuation of conditioned fear responses. Even though less consistent (Lonergan et al. 2013), these types of findings have been translated to studies in humans, where the beta-adrenergic antagonist propranolol was used to disrupt pharmacologically one-day-old fear memories (Kindt et al. 2009) as well as much older memories; that is, fear memories that underlie simple phobias for spiders (Soeter and Kindt 2015). On a cognitive level, behavioral interventions, including extinction after memory retrieval procedure, have been shown to attenuate one-day-old fear memory in rodents (Monfils et al. 2009). This finding has been translated to one-day-old (Schiller et al. 2010) and one-week-old (Steinfurth et al. 2014) memories in humans, and more recently also to older memories such as those underlying simple phobia for spiders (Björkstrand et al. 2016) and snakes (Telch et al. 2017). For further details, we refer the reader to recent overviews on memory reconsolidation literature (Lee et al. 2017; Elsey et al. 2018; Monfils and Holmes 2018).

With regard to intrusive memories, a visuospatial interference intervention administered after a reminder cue was effective in reducing intrusive memories for established (24-hour-old) memory of experimental trauma (James et al. 2015). In this study, individuals who underwent a memory reactivation procedure and performed an intervention, including *Tetris* game play, had fewer intrusive memories than a no-reactivation/no-*Tetris* group. More recently, two studies used a similar reactivation and cognitive task interference procedure, administered three days (Kessler et al. 2020) or four days (Hagenaars et al. 2017) after trauma film viewing; again, a reduction in subsequent intrusive memories was demonstrated. While both studies showed that an active control condition (verbal task) also reduced intrusions compared to a no-task control, in one study the effect was significantly larger for the visuospatial interference intervention compared to a verbal control task (Kessler et al. 2020). Interestingly, and again in line with *separate trace theories* (Lau-Zhu et al. 2019), both Kessler et al. (2020) and James et al. (2015) showed that the intervention left voluntary memory (i.e., performance on a recognition task) intact. Still, more work is warranted.

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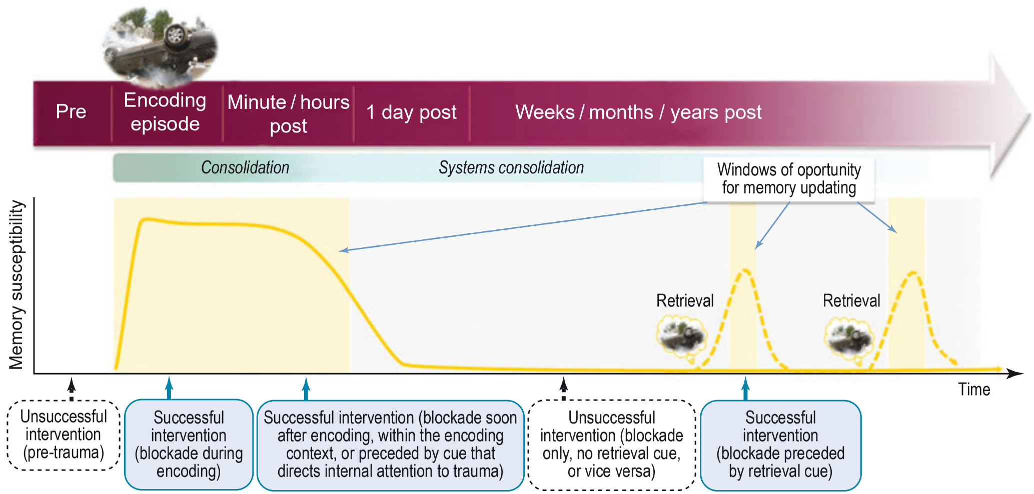

Figure 14.2 In the hours after an experience, memories are believed to go through an initial labile phase before being stored into stable long-term memory (i.e., consolidation). The purple arrow depicts different time intervals with respect to the encoding of an aversive episode. The gradients below indicate the putative processes of memory encoding and consolidation that occur during these different intervals. Recent insights suggest that certain aspects of memories, including the intrusiveness, are not necessarily permanent. Instead, they may become transiently malleable upon reactivation, rendering them susceptible to interference or updating before returning to a fixed state, a process referred to as "memory reconsolidation." This offers a second window of opportunity to interfere with consolidated memories (shown as yellow background shades), making them less intrusive. Successful interventions (blue arrows) need to be timed such that the blockade interferes with memory when it is in an active, susceptible state (indicated by the dotted yellow line), either in the first hours after trauma or at later time intervals after a retrieval procedure (e.g., reactivation through reminder cues). In the first hours after an experience, blockade procedures may also need to be preceded by cues that orient attentional resources to the event in order for procedures to successfully interfere with it (e.g., when the intervention is delivered in a context other than the one in which the trauma occurred). Unsuccessful interventions, timed when memories do not yet exist or are in a fixed state (i.e., not recently retrieved), are shown. Adapted after Visser et al. (2018).

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Real trauma memories are typically stronger and broader than aversive memories formed in the laboratory. Finding the optimal conditions and reminder cues to reactivate and render a memory labile (a first step for successful interference) is assumed to be much more challenging (Monfils and Holmes 2018) for real memories of trauma. Yet, a recent study on inpatients with complex trauma (Kessler et al. 2018) has shown promise in attenuating the intrusiveness of memories for old trauma some years previously. Twenty patients monitored the occurrence of intrusive trauma memories over the course of their admission (5–10 weeks). Weekly interventions involved a memory reminder for a selected (particularly distressing) memory, followed by 25 minutes of playing *Tetris*. A within-subjects multiple baseline design was used, in which the pre-intervention period was varied. Further, some intrusions were never targeted by the intervention. The frequency of targeted intrusive memories reduced, on average, by 64% from baseline to the postintervention phase, whereas never-targeted intrusions reduced in frequency, on average, by 11% over a comparable time period. This shows that even persistent, older memories of real-life trauma can be changed using memory interference techniques.

Despite its clear promise for clinical translation, it should be noted that a number of potential limitations and boundary conditions of reconsolidation-based clinical applications have been raised (Treanor et al. 2017; Monfils and Holmes 2018). Moreover, at present, it is not possible to attribute conclusively therapeutic gains to reconsolidation mechanisms (Elsey et al. 2018). Nevertheless, the notion of memory plasticity has proved useful in inspiring new avenues for intervention for older memories of trauma (Figure 14.2). Of particular interest to our current discussion is the potential to modify *intrusive features* of memory during time windows of memory plasticity.

To be able to interfere with older trauma memories, the memory trace has to be activated in working memory via a reminder cue. According to reconsolidation theory, there is an optimal duration for a reminder cue. When memory is retrieved via a brief learning experience (e.g., one unreinforced conditioned stimulus) it enters a labile state. However, if retrieval is prolonged (e.g., four unreinforced conditioned stimuli), the memory might enter a "limbo state," and if it is prolonged further, finally extinction. In short, if the reminder cue "dosage" (duration, instances) is too little, nothing happens (no labilization); if it is too big, the memory may enter a "limbo state" (nothing happens) or extinction learning—a new inhibitory trace is formed, fear/distress diminishes, but this effect may be temporary as it does not alter the original emotional memory trace (Lee et al. 2006; Merlo et al. 2014; Sevenster et al. 2014). All three possibilities (no labilization, limbo state, extinction learning) are different than the reconsolidation state, so the optimization of the retrieval procedure follows an inverted U-shape.

From a clinical perspective, experiencing an intrusion may even offer an opportunity to interfere with reconsolidation of this memory by engaging in

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a competing cognitive task (e.g., playing *Tetris*) within a specific time frame after the intrusion occurred (minutes). However, the question is whether spontaneous retrieval by means of experiencing an intrusion induces the required reconsolidation state, or instead any of the other states, in which case one cannot really interfere with it. This is an important empirical question which has yet to be tackled.

Recently, an experimental paradigm has been developed to capture intrusive memories as they occur in the fMRI scanner (Clark et al. 2015). After viewing scenes of traumatic events (trauma film paradigm; James et al. 2016a), particular scenes then intrude for an individual. A specific intrusive memory is triggered in the scanner by a reminder cue. The first results of experiencing an intrusive memory are shown in Figure 14.3. Understanding the neural mechanisms of experiencing an intrusive memory may yield insights for treatment (e.g., for neuromodulation strategies that could be combined with behavioral interference techniques, such as our *Tetris* procedure). Colleen Hanlon (this volume) discusses transcranial magnetic stimulation (TMS). It is possible that understanding the neural mechanisms of an intrusive event (e.g., Clark et al. 2015) alongside associated multivoxel pattern analysis (e.g., Clark et al. 2014b) will inform how best to apply TMS during an interference procedure (e.g., Kessler et al. 2018) to reduce the occurrence of intrusive memories. However, to date this has not been attempted.

Mechanisms and Mathematics

Mechanisms of cognition operate across the scales of brain organization (Bonsall et al. 2015). If multiple processes operate at different scales of organization in psychopathology (e.g., posttraumatic stress reactions or mood instability), aggregating the collective molecular and neuron interactions to higher levels of organization (such as the network level or cognitive level) might provide novel, emergent insights into the patterns associated with brain function within and among individuals.

Using mathematical approaches to scale (appropriately) across a hierarchy from cognitive and emotional processes through neuron firing patterns to candidate, molecular processes allows development of a mechanistic approach to cognition. This *mechacognitive* approach (i.e., using mathematical approaches to move down a hierarchy from symptoms to candidate, molecular processes) may allow insights through a mechanistic approach to cognition (Holmes et al. 2016b). By developing descriptions of psychopathology, it can also lead to novel approaches to understand the underlying neuroscience of brain function.

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Memory Formation, Consolidation, and Reconsolidation Is a Probabilistic Process

As discussed above, memory consolidation and memory trace are not fixed (Müller and Pilzecker 1900; McGaugh 2000). Neural changes and reorganization operate through the time period from the perception of an event to the later memory retrieval. Given that memory trace is probabilistic (changes between states) and dynamic in time (and across spatial organization in the brain), we develop mechanistic frameworks to link across scales of organization to cognition. While the molecular basis of memory involves epinephrine and cortisol and protein synthesis to affect changes in synaptic consolidation (Dudai 2004), scaling this up to focus on the neural mechanism of systems-level consolidation requires appropriate tools. We argue that this is best achieved within the frameworks and architectures of mathematics.

To bridge the gap between (intrusive) memory consolidation and treatment through a *mechacognitive* lens, we use a mathematical framework coupled to data analysis. Here, our framework focuses on intrusive memory consolidation and cognitive interference interventions including a visuospatial task (Figure 14.4). In this way we consider how perception (bringing to mind) of a traumatic event (zM) following an orientation cue (also called reminder cue for consistency with the reconsolidation literature) might lead to memory consolidating into an intrusive memory (iM) or a more neutral task memory (tM) following a task (T).

To formalize this, we consider a discrete-time Markov chain (Kemeny and Snell 1960) where memory moves through a series of states, and the probability of moving from one state to the next is only dependent on present state. Discrete-time Markov chain models underwrite many common state space models of data (e.g., latent variable models, hidden Markov models, and Markov decision processes). In our current (illustrative) application, we assume that the states are directly observable and focus on the probability transitions from one state to another and their implications for understanding therapeutic interventions. Markov chains can be described by a *directed graph* where edges are the probabilities of moving between states and vertices represent the states (Figure 14.4). The directed graph illustrates the steps needed to move from trauma memory state to consolidated task memory state. For instance, this approach allows clear assumptions to be formulated; one assumption is that trauma memory needs to be in a labile state before tasks can be undertaken and affect consolidation of the task memory. We emphasize that this is all a probabilistic process as we learn how to scale up to aggregate memory processes, driven from the molecular, short- or long-term scale to the system level (Albo and Gräff 2018) to a level of organization at the cognitive scale.

As noted, in this exemplar we consider four states: initial trauma memory state, labile memory, intrusive memory, and consolidated neutral task memory. This can be represented by the following transition matrix (N):

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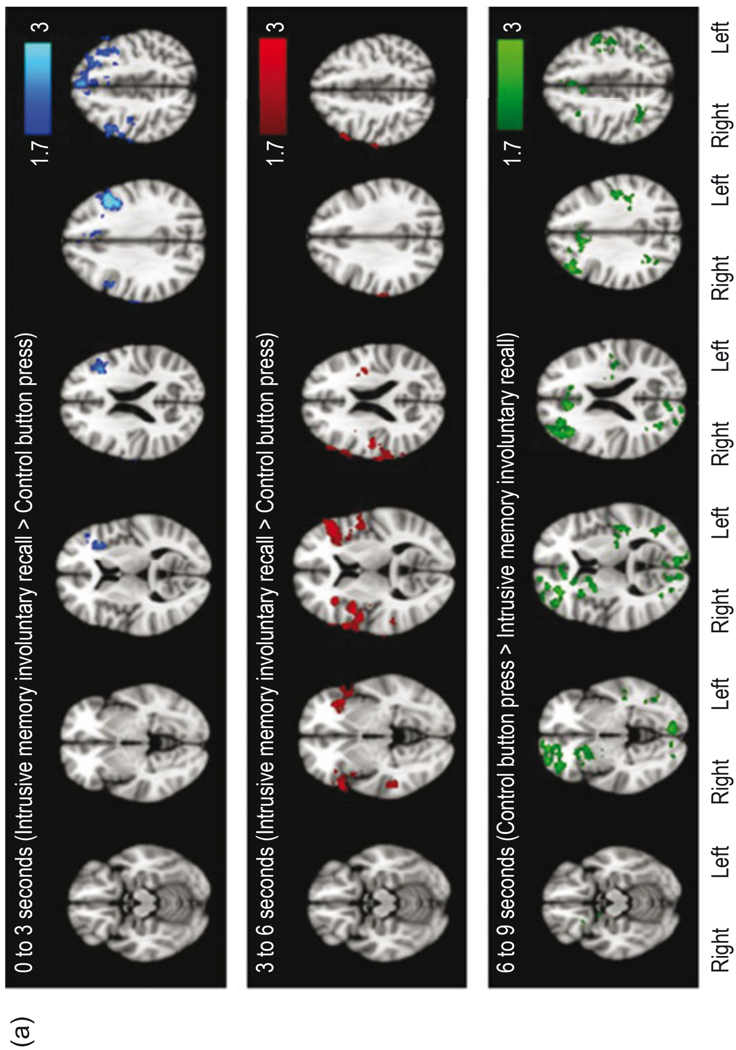

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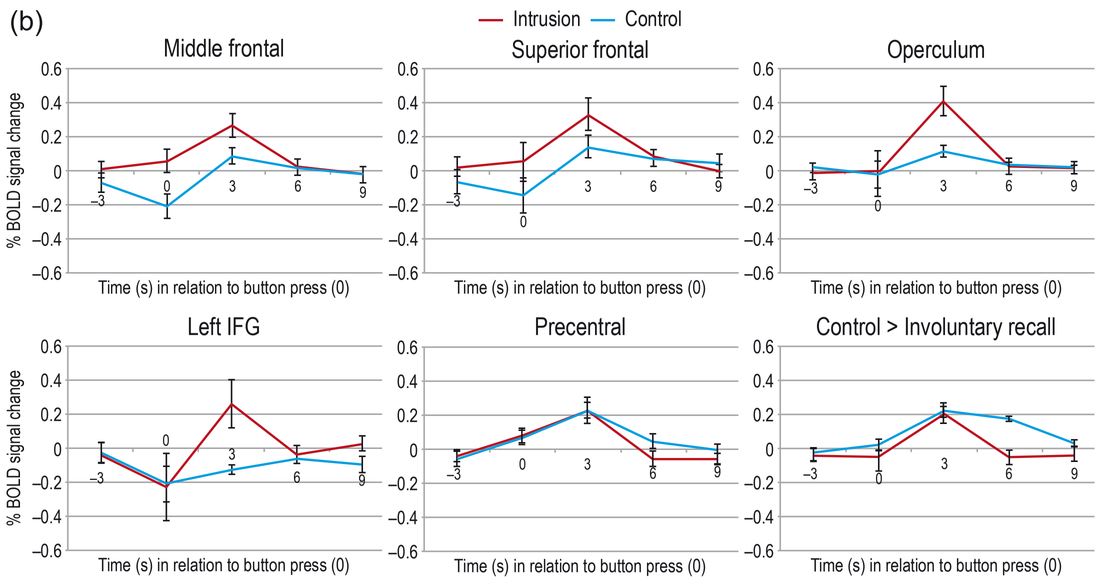

Figure 14.3 Intrusive memory involuntary recall. Top: Whole-brain analysis showing the increased blood oxygen level-dependent (BOLD) response for intrusive memory involuntary recall versus control button press group at the two time bins (0–3 s and 3–6 s in relation to the button press): note the significant differences in activation and the one time bin (6–9 s) of increased BOLD response for the control button press group versus intrusive memory involuntary recall. Bottom: Region-of-interest profile plots of the signal change observed across each time bin from –3 to +12 s in relation to the button press. Intrusive memory involuntary recall signal change activation is shown in red; control button press signal change activation in blue. Values are means; standard deviations represented by vertical bars. IFG: inferior frontal gyrus. Adapted after Clark et al. (2015).

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$$N = \begin{pmatrix} 0 & p_1 & 1-p_1 & 0 \\ 0 & p_3/(1+p_3) & p_2/(1+p_3) & (1-p_2)/(1+p_3) \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix}, \tag{14.1}$$

where p_{ij} is a transition probability (moving from a state in row i to a state in column j) such that rows of the matrix sum to one (by normalizing across the transition probabilities within a row). p_1 is the transition probability from trauma memory state to labile memory state and, in our context, is the conditional probability that memory is a labile state (lM) given a reminder cue (rC), ($\Pr(\text{lM} \mid rC)$). The probability that the reminder cue fails and intrusive memory forms for initial trauma state is $1-\Pr(\text{lM} \mid rC)$. Here, we assume that this is a logistic function, $1/(1+\exp(-\alpha))$, where α represents the strength of the reminder cue). Similarly, p_2 is the transition probability from the labile memory state to consolidated iM. In our context this is represented as a conditional probability that a task intervention affects the formation of intrusive memories ($\Pr(\text{iM} \mid T)$), and $1-\Pr(\text{iM} \mid T)$ is the probability that task intervention is effective and leads to a consolidated neutral task memory. Here we assume that

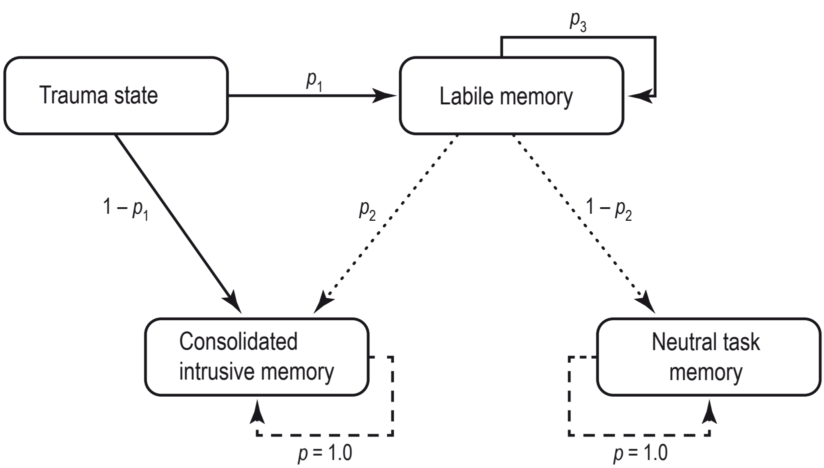

Figure 14.4 Markov chain model: Directed graph representing a Markov chain framework for exploring intrusive and more neutral task memory consolidation. Arrows (edges) represent transition probabilities between states, and boxes (nodes) represent different memory states. p_1 represents the probability that the reminder cue is successful. We describe this probability as $1/(1+\exp(-\alpha))$, where α is the strength of the reminder cue. p_2 represents the probability that task intervention is unsuccessful and parameterized here as $1/(1+T)$, where T is the strength of the task intervention. p_3 is the probability maintained in a labile state. Once memories enter an intrusive memory or neutral task memory they are fixed in these states ($p = 1.0$).

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$\Pr(\text{iM} \mid T) = 1/(1+T)$, where T is a measure of task strength. p_3 is the probability that a memory is maintained in a labile state. With these assumptions and the stochastic process framework, to investigate the role of task interventions once a memory is either in an intrusive or task consolidated state, the memory is fixed (absorbed) into this state and not amenable to further alteration. While memory consolidation and reconsolidation are dynamic processes, here we focus on the role of task interventions in affecting memory states.

Analysis of the Markov chain allows a number of different metrics to be assessed including (a) expected time in a state, (b) variance of time in a state, (c) dynamics over finite time steps, and (d) probability of absorption into a final state as a function of covariates (e.g., Kemeny and Snell 1960).

Sensitivity analysis highlights the importance of particular probability transitions (or more specifically drivers of probability transitions) and the factors influencing memory consolidation at different levels of organization. Here, analysis of the Markov chain reveals that the *labile memory state* is transient. Expected time in this labile memory state is a function of reminder cue probability (p_1) and probability of staying in the labile memory state (p_3) (Figure 14.5a). Increases in the probability of keeping the memory labile (p_3), and increases in reminder cue strength (α) lead to longer expected times of memory in a labile state. However, the uncertainty (variance) in the length of time a memory is labile is most likely influenced by the probability of keeping the memory labile (p_3) rather than reminder cue strength, and most uncertainty in the length of time a memory is labile is greatest for low reminder cue strengths and high probabilities of keeping the memory labile (Figure 14.5b).

Potentially more important is the *probability that intrusive or task memories consolidate*; that is, since this is an absorbing Markov chain with two end states, whether memories persist in the iM or tM state. Analysis of the Markov chain reveals that the probability that an iM consolidates following trauma is:

$$\Pr(\text{iM} \mid \text{trauma}) = (1-p) + p_1 p_2. \tag{14.2}$$

Equation 14.2 expresses the probability that an iM consolidates given that the reminder cue fails $(1-p_1)$ or the probability that the reminder cue is successful and that the task intervention is not successful ($p_1 p_2$). For our parameterization, where $p_1 = 1/(1+\exp(-\alpha))$ and $p_2 = 1/(1+T)$:

$$\begin{aligned} \Pr(\text{iM} \mid \text{trauma}) &= \left(1-\left(\frac{1}{1+exp(-\alpha)}\right)\right) + \frac{1}{(1+exp(-\alpha))(1+T)} \\ &= \frac{1+exp(-\alpha)+T}{1+exp(-\alpha)+T+exp(-\alpha)T}. \end{aligned} \tag{14.3}$$

The terms that contribute to this conditional probability can also be determined intuitively by looking at Figure 14.4 and tracing the paths from the trauma state to the intrusive memory state, accumulating the probabilities along all

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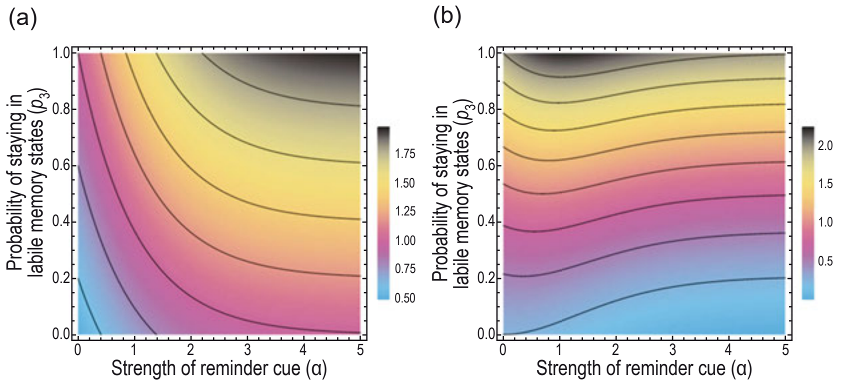

Figure 14.5 Markov chain analysis of transient memory states. (a) Expected times and (b) variances in expected times in labile memory states in terms of strength of reminder cue (α) and the probability of staying in the labile memory state (p_3). Strong reminder cues and high probability of maintaining a memory in a labile state favor long retention times in this transient (labile) memory state. However, most uncertainty in expected retention times is observed for low reminder cue strengths and high probability of maintaining a memory in a labile state.

direct and indirect paths. The marginal change in the probability of iMs is more sensitive to changes in the probability of task success (p_2) than the reminder cue success probability (p_1), as the following inequalities for the change in $d(\Pr(\mathrm{iM}\,|\,trauma)/dp_{\mathrm{i}}$ can be shown to hold:

$$\frac{d\left(\Pr\left(\mathrm{iM}\,|\,\mathrm{trauma}\right)\right)}{dp_2} = p_1 > \left(p_2 - 1\right) = \frac{d\left(\Pr\left(\mathrm{iM}\,|\,\mathrm{trauma}\right)\right)}{dp_1}. \qquad (14.4)$$

The above inequality holds from our parameterization of p_1 and p_2:

$$1 + \frac{1}{1+\exp\left(-\alpha\right)} > \frac{1}{1+T}, \qquad (14.5)$$

which, again, are the probabilities along the path from trauma to task memory consolidation (Figure 14.4). The probability that a task memory consolidates is:

$$\Pr\left(\mathrm{tM}\,|\,\mathrm{trauma}\right) = p_1\left(1 - p_2\right), \qquad (14.6)$$

which is the probability that the reminder cue is successful (p_2), and the task intervention is successful ($1-p_2$). Again, the terms that contribute to this conditional probability can also be determined intuitively from Figure 14.4, tracing paths from the trauma state to the consolidation state, and accumulating the probabilities along all direct and indirect paths. Two key predictions from this analysis are as follows:

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1. The probability of maintaining a memory in a labile state (p_3) has no effect on the probability of iMs or tMs consolidating.
2. Most importantly, the probability of a successful reminder cue is critical: if this cue is unsuccessful (p_1 tends to zero), then the probability of an intrusive memory consolidating tends to 1 and the probability of consolidated task memory tends to 0.

Formulating memory consolidation as a stochastic process, aggregating across scales of organization, allows systems-level mechanisms associated with cognition to be investigated. Next, we briefly show how the model can be validated against empirical observations and/or experiments.

Model Validation: Statistical Approaches

Determining the accuracy and applicability of a mathematical framework centers around model validation. Validating a model involves appropriate parameterization, goodness of fit to data, uncertainty quantification, and prediction. Linking a mechanistic model, such as our Markov chain, to data involves statistics and statistical modeling.

While full model validation is beyond the scope of what we present here, we show ways in which Markov chains can be parameterized from trauma and iM studies and the likely predictions that arise from this parameterization, deriving the conditional probabilities that (a) a reminder cue places a memory in a labile state and (b) task intervention affects the probability of intrusive memories has been approached empirically (e.g., James et al. 2015; Iyadurai et al. 2018, 2019; Lau-Zhu et al. 2019; Visser et al. 2018).

To determine the efficacy of a reminder cue, a binary regression is needed with probability of a successful reminder cue as a response with a set of explanatory covariates. To determine the conditional probability that task affects probability of memory consolidation, we have advocated appropriately addressing statistical issues, such as correlation structures (James et al. 2015; Iyadurai et al. 2018) and/or heterogeneity (Iyadurai et al. 2019). One way to derive appropriate probability estimates on the efficacy of a task is through the use of mixture models (Cameron and Trivedi 2013), where statistical modeling of zero and nonzero intrusive memories (from diary data) is considered differently.

Mixture models represent the nonzero and the zero observations separately with two statistical models. First is to ask: Are the zero counts generated because of the iM/trauma process or something else (perhaps to do with data collection)? This is a Bernoulli process with a probability (say p, where this probability is to be determined by the set of explanatory variables) that the zeros are generated by alternative processes than those under observation. So $(1 - p)$ is the probability that the zeros are generated by the iM/trauma process. As iMs are count data (e.g., the number of intrusive memories per day), the

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nonzeros are modeled assuming Poisson errors. The probability of j intrusive memories can then be represented by the following mixture model:

$$\Pr\left(\mathrm{iM}=j\right)=\begin{cases} p+\left(1-p\right)\exp\left(-u\right) & \text{if } j=0 \\ \left(1-p\right)\dfrac{u^{iM}\exp\left(u\right)}{\mathrm{iM}!} & \text{if } j>0 \end{cases}. \tag{14.7}$$

The mixture model applies a binary/binomial regression to determine p (top line, right-hand side of Equation 14.7) and a Poisson regression to model the nonzero counts (bottom line, right-hand side of Equation 14.7).

The binomial and Poisson components of the regression can consider different covariates (e.g., task/no-task, task strength, task quality) to determine probability of intrusive memories and appropriately address heterogeneity generated by an overinflated number of zeros.

To illustrate this approach for data analysis and application to the Markov chain model, a zero-inflated Poisson model analysis was undertaken on a group of patients involved in traumatic road traffic; these patients took part in a cognitive interference intervention that included a reminder cue and a visuospatial task (for details, see Iyadurai et al. 2018). This analysis reveals that the overall probability (across this group of patients) of a successful intervention $(1-p_2)$ and no iMs is 0.542 (Figure 14.6). Together with the Markov chain analysis, this empirical estimate of no iMs (i.e., zeros), given a cognitive task, predicts that the probability of a consolidated task memory across this group of patients would range from 0 to 0.542 (depending on the probability of a successful reminder cue).

The opportunities for using mathematical approaches for linking across mechanisms of cognition, different illnesses and traumata, modalities of perception, and individual patients is a nascent approach. However, we believe this *mechacognitive* approach has value along the continuum from the basic through to clinical aspects of neuroscience and will provide a fuller understanding of memory consolidation.

Conclusions

Recent findings on intrusive mental images, reviewed in the first part of this chapter, as well as the mathematical model on intrusive memory consolidation and visuospatial interference interventions, introduced in the second part, give reason to take a step back and think about how current psychological interventions might be improved. We have proposed that to progress in this regard, we need to know more about specific processes involved in intrusive thinking and adopt a targeted treatment approach (Iyadurai et al. 2019). We conclude by raising the following questions to invigorate discussion on how we can make future psychological interventions more precise and effective.

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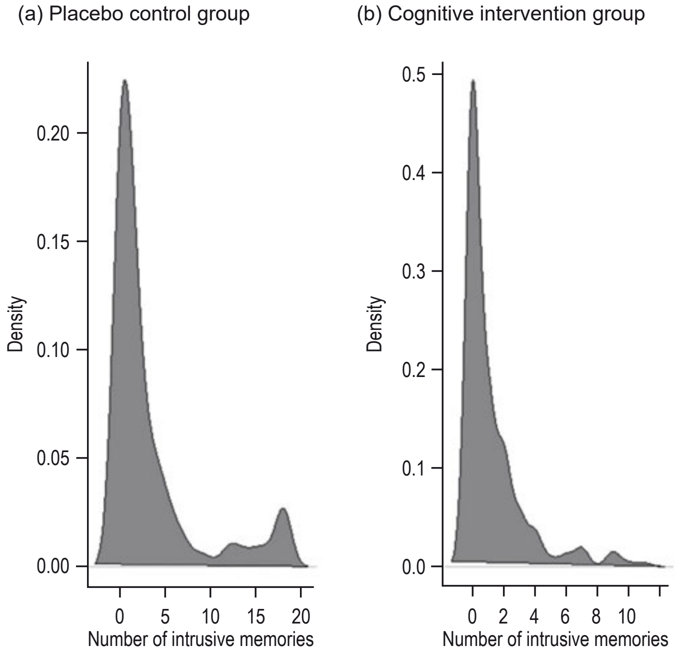

Figure 14.6 Density distribution of intrusive memories (adapted after Iyadurai et al. 2018) for (a) the attention placebo control group and (b) the active cognitive intervention (reminder cue + visuospatial interference task) group. Statistical analysis on (b), using a zero-inflated Poisson intercept-only model (Equation 14.7), reveals that the nonzero counts have an intercept that is significantly different from zero (intercept = 0.908 ± 0.144 (SE), z-value = 13.72, $p < 0.001$), while the zero counts do not (intercept = 0.0006 ± 0.144, z-value = 0.0004, $p = 0.997$). The expected probability of no intrusive memories in the active intervention group, determined from Equation 14.7 and across this group of patients, is 0.542.

What if we specifically target intrusive thinking as a primary outcome rather than a multitude of symptoms of a given disorder? Intrusive imagery is common across psychological disorders and appears to be an important transdiagnostic factor regardless of specific diagnosis (Iyadurai et al. 2019). By looking specifically at intrusive imagery rather than broad and fuzzy assemblies of symptoms clusters, we may be able to radically change current treatment approaches in mental health. For instance, while we may not be able to treat PTSD or depression reliably as a whole (especially at scale), we may be able to target a specific issue, such as intrusive memories, that is common to both disorders. This could also cross-fertilize treatment approaches across different disorders. Interventions targeting intrusive memories of trauma might inform us about potential methods to target intrusive thoughts in depression, as has been the case with imagery

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rescripting. Developing a simple intervention that is precise and can be delivered exactly to the intrusion trace may be a galvanizing aim for experimental medicine across disorders.

What if we can target involuntary intrusive memories yet leave voluntary memory intact? One of the most heated debates in the literature on intrusive memories involves whether involuntary and voluntary memories of an event are best represented by single or separate memory trace accounts (Lau-Zhu et al. 2019). Based on a recent series of carefully controlled experiments investigating this question, we argue that memory is in fact dissociable, and involuntary intrusive memories stand out from voluntary memories. This dissociation has important implications in clinical settings as well as for society. We need to develop psychological interventions that can prevent involuntary distressing images from intruding on one's mind while still enabling people to voluntarily recall information about the event (e.g., to be able to testify regarding a traumatic event in a court of law). Visuospatial interference interventions are promising because they appear to target selectively and precisely the intrusive memory trace while leaving the voluntary memory intact (Lau-Zhu et al. 2019). A successful recovery posttrauma from a clinical perspective is being able to talk about the traumatic event(s) when one decides to or needs to, but not to have them continually intrude in one's mind against one's will.

What if we are able to prevent new intrusive memories as well as tackle older ones? In addition to preventing the consolidation of "new" intrusive memories with visuospatial interference interventions directly after a traumatic event (the same day), we argue that a similar type of intervention could be adapted to target "old" intrusive memories. Importantly, when targeting older trauma memories (24 hr to several years after the traumatic event), studies have indicated that an approximately 10-minute gap has to be added between reminder cue and intervention, supposedly to make the memory trace malleable (Agren et al. 2012; Schiller et al. 2013; James et al. 2015; Kessler et al. 2018, 2020), although more research on this gap is needed. Methodologically, this opens experimental designs to study visuospatial interference interventions. For example, where there are older intrusive memories of several different events, one could target single intrusive images one after the other (i.e., one at a time) and compare frequency and distress of targeted and nontargeted intrusions over time (Kessler et al. 2018). Targeting old intrusive memories is clearly important for vulnerable patient groups (e.g., refugees). Creating rational approaches that look more like computer game play may be useful for those who do not seek traditional psychological help because of perceived stigma. Developing a brief, easily accessible, and nonstigmatized cognitive intervention that could potentially be self-administered would fill an important gap to reach such vulnerable patient groups (Holmes et al. 2018).

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What if we could go global and target large sections of populations suffering trauma? Trauma is a global health issue, and to address this we need innovative interventions that can be scaled up to overcome current barriers in psychological treatment. For instance, it is impossible for traditional psychological treatments to be delivered to the large number of people who need them globally due to the lack of trained psychologists. Thus, we need interventions that are of low intensity, require few resources to deliver, are culturally adaptive, and accessible to many (Iyadurai et al. 2019). Approaches such as the cognitive interference intervention (if shown effective in large-scale clinical trials) could potentially be readily delivered by nonspecialists or even be self-administered. Thus, an important aspect of bringing an intervention to a global level is how to train people successfully with different background knowledge in delivering the intervention (Holmes et al. 2018). Relatedly, at the global level, prevention may ultimately be as important as a cure. Rather than treating psychological disorders after they have developed and caused burden on the individual and society (in terms of suffering, health care costs, and loss of work force), selective prevention for high-risk groups (e.g., firefighters, paramedics, emergency department staff, war survivors) or universal prevention (i.e., everyone experiencing trauma could be treated no matter if they would actually develop intrusive images or not) would be a useful way to combat maladaptive intrusive thinking.

What if we could prevent intrusive memories as well as boost positivity at the same time? We need to find a way to make interventions as effective as possible while keeping them simple. Rather than simply aiming for a reduction of intrusive memories, we might also want to boost positivity, if we could find a simple way to combine this within the same task procedure (e.g., increase optimistic mental images of the future and direct attention to adaptive information; see Kress and Aue 2017). Positive imagery and optimism can be two main targets, potentially at once. Notably, the mathematical model on memory (re)consolidation and task interference introduced here could help find the best way to test this (and related) questions. For instance, the model raises the intriguing possibility that, at least in some situations, two weak tasks can lead to a stronger outcome than one strong task, and this may help clarify at which point in time specific interventions are most effective.

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